Remarks

Applicants have carefully considered this Application in connection with the Examiner's Office Action and respectfully request reconsideration of this Application in view of the following remarks.

I. Status of Claims and Amendments

Applicants appreciate the Examiner's acknowledgment of the Response to Restriction Requirement which was filed on 8 September 2011 (the "Response"). As a result of the Response, only claims 20-24 and 30 are under consideration in the instant office action.

Applicants also appreciate the Examiner's remarks with regard to the conflicting status of several claims. Upon review of the Response, it was noted that Applicants inadvertently provided a claim listing in which non-elected claims were cancelled, namely Claims 17-19, 25-27, 29 and 33-35 as evidenced by the fact that Claims 17-19, 25-27, 29 and 33-35 were stated to be withdrawn, as opposed to cancelled, within the Remarks section of the Response. (See page 4 of the Response.) Although Applicants had clearly indicated in the Remarks section of the Reponse which claims were to be pursued, the inadvertent cancellation of Claims 17-19, 25-27, 29 and 33-35 precluded the Examiner from properly withdrawing claims drawn to non-elected inventions and species. As Applicants wish to maintain the non-elected inventions and species of record and allow the Examiner to properly withdraw those non-elected inventions and species, new claims 36-45 have been added.

Claims 36-40 are identical to previously filed claims 17-19, 27, and 29, which the Examiner had initially identified as Group I in the Office Communication of 8 August 2011 (the "Restriction Requirement"). Claims 41 and 42 are identical to previously presented claims 25 and 26, which the Examiner had initially identified as Group III in the Restriction Requirement. Claim 43 is identical to previously filed claim 33, which the Examiner had initially identified as Group IV in the Restriction Requirement. Claim 44 is identical to previously filed claim 34, which the Examiner had initially identified as Group

V in the Restriction Requirement. Claim 45 is identical to previously filed claim 35, which the Examiner had initially identified as Group VI in the Restriction Requirement.

Support for the amendments can be found, at least in part, in the Preliminary Amendment filed on July 20, 2006 and in the following locations in the specification of international application PCT/EP2005/001166 (the "Specification"), of which the present application is a National-Stage entry: (1) the first two full paragraphs of page 2; (2) the third full paragraph of page 3; (3) all of page 4; (4) the first full paragraph of page 7; (5) the first full paragraph of page 8; (6) the fourth paragraph of page 18; (7) the fifth paragraph of page 19; (8) the first, third and fifth full paragraphs of page 28; (9) the first, second and third full paragraphs of page 29; and (10) the examples and claims. As the subject matter of claims 36-45 has been previously claimed no new matter is added as a result of this Amendment. Applicants respectfully request that the Examiner enter new claims 36-45 into the record, and then formally withdraw them as drawn to non-elected inventions and species.

II. Priority

Applicants appreciate the Examiner's acknowledgment of priority under 35 U.S.C. 119(a)-(d) based on UK application GB 040269.5, filed on 6 February 2004.

III. Information Disclosure Statement

Applicants appreciate the Examiner's acknowledgment of the information disclosure statement filed on 20 July 2006 and consideration of the documents cited therein.

IV. Rejection under 35 U.S.C. §103(a)

The Examiner has rejected claims 20-24 and 30 under 35 U.S.C. §103(a) as being unpatentable over Lang (WO 99/61025) and Gerspacher (US Patent 6,319,917). Applicants respectfully traverse this rejection.

The present inventions under consideration relate to novel pharmaceutical compositions in which the active agent is a 5-aryl-4(R)-arylcarbonylamino-pent-2-enoic acid amide substance P antagonist, in particular (4R)-4-[N'-methyl-N'-(3,5-bistrifluoro-methyl-benzoyl) amino]-4-(3,4-dichlorobenzyl)-but-2-enoic acid N-[(R)-epsilon-caprolactam-3-yl]-amide, that are useful for the treatment and prevention of respiratory diseases including asthma and chronic obstructive pulmonary disease, bowel disorders including irritable bowel syndrome (IBS), urinary incontinence, and cough. (See Specification, page 1.) 5-aryl-4(R)-arylcarbonylamino-pent-2-enoic acid amide substance P antagonists, such as those disclosed in WO 98/07694, present highly specific difficulties in relation to administration generally and galenic compositions in particular, including in particular problems of drug bioavailability and variability in inter- and intra-patient dose response, necessitating development of a non-conventional dosage form. (See Specification, page 1.) In accordance with the present invention it has now surprisingly been found by Applicants that stable pharmaceutical compositions with 5-aryl-4(R)-arylcarbonylamino-pent-2-enoic acid amide substance P antagonists, having particularly interesting bioavailability characteristics and reduced variability in inter- and intra-subject bioavailability parameters, are obtainable. These novel compositions have been found to meet or substantially reduce the difficulties encountered previously. It has been shown that the compositions of the invention may enable effective dosaging with concomitant enhancement of bioavailability as well as reduced variability of absorption/bioavailability levels for and between individual patients. (See Specification, page 1.)

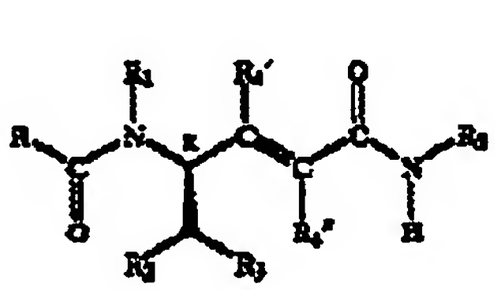
The Lang specification discloses compositions containing a piperidene substance P angatonist and sets forth several embodiments of the inventions claimed therein. In one embodiment, Lang teaches a spontaneously dispersible pharmaceutical composition comprising a piperidine substance P antagonist. (See Lang, page 2.) In another embodiment, Lang teaches a spontaneously dispersible pharmaceutical composition comprising a piperidine substance P antagonist as the active agent, and a carrier medium comprising: (i) a hydrophilic component, and (ii) a surfactant. (See Lang, page 3.) In a third embodiment, specifically identified by the Examiner on page 5 of the present Office Action, Lang teaches the active agent of the spontaneously

dispersible pharmaceutical composition is a piperidine substance P antagonist, such as (2R, 4S)-N- (1-(3,5-bis-(trifluoromethyl)-benzoyl)-2- (4-chlorobenzyl)- 4-piperidinyl)-quinoline-4-carboxamide, and the carrier medium comprises: (i) a hydrophilic phase, (ii) a lipophillic phase, and (iii) a surfactant. (See Lang, page 9.) Since Lang only discloses piperidine substance P antagonists, the Applicants' claimed compositions in Claims 20-24 and 30, all of which contain (4R)-4-[N'-methyl-N'-(3,5-bistrifluoro-methyl-benzoyl) amino]-4-(3,4-dichlorobenzyl)-but-2-enoic acid N-[(R)-epsilon-caprolactam-3-yl]-amide instead of a piperidine substance P antagonist, are not obvious in view of Lang alone.

Applicants respectfully direct the Examiner's attention to the fact that, for all embodiments in Lang in which a carrier medium is specifically identified, Lang specifically requires that a hydrophilic component or phase be present. Applicants' Claims 20, 22, 23, 24 and 30 differ from such Lang embodiments in that a hydrophilic component is not recited in the claims as an element of the carrier medium. Therefore, Applicants' compositions claimed in Claims 20, 22, 23, 24 and 30 differ from such embodiments in Lang in two respects, namely they do not contain a piperidine substance P antagonist and a hydrophilic component is not essential to the claimed compositions.

The Gerspacher specification states that compounds of the following formula:

Compounds of formula I



wherein R_1, R_2–R_3, R_4', R_4'' and R_5 are as defined in the description, have valuable pharmaceutical properties and are effective especially as NK1 and NK2 antagonists. They are prepared in a manner known per se.

are effective as antagonists of NK1 and NK2 receptors. Gerspacher indicates that the action of compounds of formula 1 on NK1 and NK2 receptors renders them useful in the prevention, treatment, and diagnosis of a variety of diseases, including bronchial and

allergic asthma; further, Gerspacher states that these compounds are antagonists of substance P. (See Gerspacher, col. 3, lines 28-65.) The Examiner notes that example 22 of Gerspacher teaches the preparation of (4R)-4-[N'-methyl-N'(3,5-bistrifluoromethyl-benzoyl)-amino]-4-(3,4-dichlorobenzyl)-but-2-enoic acid N-[(R)-epsilon-caprolactam-3-yl]-amide. (See Office Action, page 7.)

The Examiner states that it would have been prima facie obvious at the time the invention was made for one of ordinary skill in the art to modify the composition of Lang by substituting the piperidine based substance P antagonist such as (2R,4S)-N-(1-(3,5-bis(trifluoro-methyl)-benzoyl)-2-(4-chlorobenzyl)-4-piperidinyl)-quinoline-4-carboxamide with the substance P antagonist (4R)-4-[N'-methyl-N'(3,5-bistrifluoromethyl-benzoyl)-amino]-4-(3,4-dichlorobenzyl)-but-2-enoic acid N-[(R)-epsilon-caprolactam-3-yl]-amide recited in the Applicants' invention and disclosed in Gerspacher. (See Office Action, the paragraph bridging pages 7 and 8.) The Examiner argues that one skilled in the art would have been motivated to make the substitution "because the two P antagonists are functionally equivalent as P antagonists." (See Office Action, page 9.)

However, the present invention relates to the <u>formulation</u> of (4R)-4-[N'-methyl-N'(3,5-bistrifluoromethyl-benzoyl)-amino]-4-(3,4-dichlorobenzyl)-but-2-enoic acid N-[(R)-epsilon-caprolactam-3-yl]-amide as a pharmaceutical, <u>not to its biological function</u>. Whether a certain formulation is preferable for a medicine is not an issue of biological function, but instead is reflective of the structure and the chemical characteristics of the candidate compound. In other words, similarity in biological function alone is not sufficient to establish the motivation for substituting an active ingredient having a particular biological function for a structurally different compound with the same biological function in a particular formulation. Therefore one of ordinary skill in the art would not be motivated to substitute the compound of Gerspacher for a piperidine compound in the Lang formulation simply because both compounds are substance P antagonists.

The Examiner further argues that one of ordinary skill in the art would have had a reasonable chance of success in combining the teachings of Lang and Gerspacher

"because both references teach pharmaceutical compositions containing P antagonists." (See Office Action, page 9.) Simply because two compounds have the same biological function does mean that one of ordinary skill in the art would have a reasonable expectation of success if the references are combined as proposed by the Examiner, namely by substituting the (4R)-4-[N'-methyl-N'(3,5-bistrifluoromethyl-benzoyl)-amino]-4-(3,4-dichlorobenzyl)-but-2-enoic acid N-[(R)-epsilon-caprolactam-3-yl]-amide compound of Gerspaher for the structurally different piperidene compound in the Lang formulation.

Additionally, the Examiner's argument with respect to Claim 30, which claims a microemulsion, is premised on the assumption that any substance P antagonist compound could be advantageously formulated as a microemulsion. (In the Lang embodiment cited by the Examiner, it is stated that the composition may be in the form of a microemulsion. (See Lang, page 10.)) However, this does not reflect the knowledge in the art at the time of invention. While self-emulsifying systems constitute one possible option to enhance the bioavailability of a given drug, they are not the only method for increasing bioavilability. For example, Hauss et al (American Pharmaceutical Review, 2002; cited in the International Search Report) provides a variety of possible approaches for enhancing the bioavailability of poorly water soluble drugs. (A copy of the Hauss article was submitted with an Information Disclosure Statement and has been considered by the Examiner.)

Hauss teaches salt selection, prodrug synthesis, and particle size-reduction as possible approaches for enhancing bioavailability of poorly soluble drugs. (See Hauss, page 22.) Similarly, Hauss teaches solubilization in an excipient matrix and inclusion complexes. (See Hauss, page 24.) For lipid-based formulations, Hauss discusses two main approaches, namely self-emulsifying drug delivery systems (SEDDS) and microemulsions. (See Hauss, page 26, left column.) Given the variety of methodologies for enhancing bioavailability described above, one cannot presume that merely because a methodology is known that it is preferred or will work for a particular compound.

To that end, Applicants respectfully direct the Examiner's attention to the Hauss statement that "[d]isadvantages of a ME [microemulsion], in addition to the relative complexity of the formulation development process, include potential toxicity due to surfactant and co-surfactant concentrations and types as well as potential destruction of the emulsion by dilution in the GI tract." (See Hauss, page 26.) By listing the disadvantages connected with the use of microemulsions, Hauss would have deterred a person of ordinary skill in the art from using microemulsions as the formulation of choice for poorly soluble drugs.

Furthermore, Hauss raises doubts about the effects of a microemulsion formulation on bioavailability. Hauss teaches that the mechanisms by which lipids enhance absorption of hydrophobic drug molecules are not fully understood. (See Hauss, page 24.) Additionally, Hauss provides that the "bioavailability-enhancing performance of most oral lipid-based formulations is dependent on the ability of the formulation to maintain the drug in solution within the excipient matrix." (See Hauss, page 24.) It is clear, therefore, that there are additional factors that must be taken into account when improving bioavailability.

The teachings of Hauss described above thus preclude a determination that the use of microemulsions necessarily improves bioavailability of a given drug or that one of ordinary skill in the art would have had a reasonable expectation of success in combining the references as suggested by the Examiner.

The Applicants found that the formulation of (4R)-4-[N'-methyl-N'(3,5-bistrifluoromethyl-benzoyl)-amino]-4-(3,4-dichlorobenzyl)-but-2-enoic acid N-[(R)-epsilon-caprolactam-3-yl]-amide as a microemulsion resulted in an unexpected improvement of the bioavailability of the compound. Applicants direct the Examiner's attention to the surprising results which were achieved when they formulated (4R)-4-[N'-methyl-N'(3,5-bistrifluoromethyl-benzoyl)-amino]-4-(3,4-dichlorobenzyl)-but-2-enoic acid N-[(R)-epsilon-caprolactam-3-yl]-amide as a microemulsion. The formulation of (4R)-4-[N'-methyl-N'(3,5-bistrifluoromethyl-benzoyl)-amino]-4-(3,4-dichlorobenzyl)-but-2-enoic acid N-[(R)-epsilon-caprolactam-3-yl]-amide as a microemulsion using the carrier

medium of the invention resulted in significantly enhanced plasma levels of the drug in a dog study compared to a classical formulation as a powder in a capsule (see page 35 of the Specification and Figure 1/1 of the Specification.) These surprising and unexpected results support the non-obviousness of the Applicants' claimed inventions.

Based on the foregoing, one of ordinary skill in the art would not be motivated to combine the references as suggested by the Examiner nor would one of ordinary skill in the art have a reasonable expectation of success if the references were combined as suggested by the Examiner. As a result, the Applicants respectfully submit that the Examiner has not established a prima facie case of obviousness.

V. Conclusion

In light of the foregoing arguments, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. §103 rejection of Claims 20-24 and 30 and advance the application to allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration to this Reply is respectfully requested.

Respectfully submitted,
Montgomery, McCracken, Walker & Rhoads, LLP

David J. Roper
Attorney for Applicants
Registration No. 32,753

Date: 15 February 2012
123 South Broad Street
Philadelphia, PA 19109-1099
Tel: (610) 889 -2224